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ORIGINAL REPORT

Multicenter Analysis of 80 Solid Organ Transplantation Recipients With Post-Transplantation Lymphoproliferative Disease: Outcomes and Prognostic Factors in the Modern Era

Andrew M. Evens, Kevin A. David, Irene Helenowski, Beverly Nelson, Dixon Kaufman, Sheetal M. Kircher, Alla Gimelfarb, Elise Hattersley, Lauren A. Mauro, Borko Jovanovic, Amy Chadburn, Patrick Stiff, Jane N. Winter, Jayesh Mehta, Koen Van Besien, Stephanie Gregory, Leo I. Gordon, Jamile M. Shammo, Scott E. Smith, and Sonali M. Smith

From the Division of Hematology/Oncology, Robert H. Lurie Comprehensive Cancer Center; Departments of Preventive Medicine and of Pathology, Division of Solid Organ Transplantation, Northwestern University Feinberg School of Medicine; Division of Hematology/Oncology, University of Chicago; and Hematology Department, Rush University Medical Center, Chicago; and Division of Hematology/Oncology, Loyola University Medical Center, Maywood, IL.

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Corresponding author: Andrew M. Evens, DO, MSc, Division of Hematology/Oncology, 676 N St Clair S, Suite 850, Chicago, IL, 60611; e-mail: a-evens@northwestern.edu.

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ABSTRACT

Purpose
Adult post-transplantation lymphoproliferative disease (PTLD) has a reported 3-year overall survival (OS) of 35% to 40%. The impact of rituximab on the outcome of PTLD is not well defined.

Methods
We examined the clinical features and outcomes among a large cohort of solid organ transplantation (SOT) –related patients with PTLD who were recently treated at four Chicago institutions (from January 1998 to January 2008).

Results
Eighty patients with PTLD were identified who had a median SOT-to-PTLD time of 48 months (range, 1 to 216 months). All patients had reduction of immunosuppression as part of initial therapy, whereas 59 (74%) of 80 patients received concurrent first-line rituximab with or without chemotherapy. During 40-month median follow-up, 3-year progression-free survival (PFS) for all patients was 57%, and the 3-year overall survival (OS) rate was 62%. Patients who received rituximab-based therapy as part of initial treatment had 3-year PFS of 70% and OS 73% compared with 21% ($P < .0001$) and 33% ($P = .0001$), respectively, without rituximab. Notably, of all relapses, only 9% (4 of 34 patients) occurred beyond 12 months from PTLD diagnosis. On multivariate regression analysis, three factors were associated with progression and survival: CNS involvement (PFS, 4.70; $P = .01$; OS, 3.61; $P = .04$), bone marrow involvement (PFS, 2.95; $P = .03$; OS, 3.14; $P = .03$), and hypoalbuminemia (PFS, 2.96; $P = .05$; OS, 3.64; $P = .04$). Furthermore, a survival model by multivariate CART analysis that was based on number of adverse factors present (ie, 0, 1, ≥ 2) was formed: 3-year PFS rates were 84%, 66%, 7%, respectively, and 3-year OS rates were 93%, 68%, 11%, respectively ($P < .0001$).

Conclusion
This large, multicenter, retrospective analysis suggests significantly improved PFS and OS associated with early rituximab-based treatment in PTLD. In addition, clinical factors at diagnosis identified patients with markedly divergent outcomes.

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INTRODUCTION

It has been 40 years since the first report of post-transplantation lymphoproliferative disorder (PTLD).[1] Since that time, PTLD has remained one of the most morbid complications associated with solid organ transplantation (SOT).[2-5] Furthermore, survival rates have remained poor, with mortality rates ranging from 50% to 70% in most studies.[2,6-12] A therapeutic approach used for the past 20 years is reduction of immune suppression (RI).[13] This is an important concept in the treatment of PTLD, although responses occur in less than half of patients, and durable remissions are uncommon.[5,9,14]

The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for immunocompetent diffuse large B-cell lymphoma improved long-term survival rates to approximately 60% to 65%.[15-17] The impact, if any, of rituximab in the outcome of PTLD is not well defined. Single-agent rituximab was evaluated in two phase II PTLD studies for patients who experienced

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failure with RI and who had overall response rates of 42% and 73%.[18,19] Other series have reported on the use of rituximab in PTLD,[10,20-23] although each of these reports were small. Additionally, the vast majority of reports have examined rituximab as second-line therapy (or later) after failure of RI.

Most PTLD prognostic analyses have been single-institution studies examining outcomes over multiple decades, during which time diagnostic techniques and treatment options evolved tremendously. In addition, little is known about the significance of previously identified prognostic markers in patients with PTLD who were treated with rituximab-based regimens. In two of the larger PTLD studies reported before widespread rituximab usage, Leblond et al[11] and Ghobrial et al[9] identified several prognostic factors associated with inferior survival, including poor performance status (PS), greater than one extranodal site, and monomorphic subtype. Fewer than 10% of patients in these series, however, received rituximab as part of initial PTLD therapy. Given the shift in treatment paradigms to incorporate rituximab into first-line treatment for B-cell lymphomas, prior prognostic models need to be reconsidered.

We report here a multicenter collaboration that investigated a cohort of 80 patients with PTLD who were treated during a recent 10-year period. The majority of patients (80%) received rituximab-based treatment, most as a component of first-line therapy together with RI. We investigated the clinical and disease-related characteristics and associated these factors with outcomes, including creation of a new prognostic survival model.

PATIENTS AND METHODS

We conducted a multicenter, retrospective analysis of patients diagnosed with PTLD after SOT at four academic medical centers in Chicago, IL: Northwestern University, University of Chicago, Rush University, and Loyola University. All patients with PTLD were consecutively diagnosed between January 1998 and January 2008 and occurred in adult patients (ie, age $\geq$ 18 years). The study was approved by the institutional review boards of all institutions. All PTLDs were confirmed by expert hematopathologists at each individual institution, as described by WHO.[24]

Ninety-one eligible patients were identified. Eighty had complete pathologic and clinical data and were entered onto a centralized database (Northwestern, n = 35; University of Chicago, Loyola, and Rush, n = 15 each). Eleven patients were excluded because of second opinion/inadequate follow-up data (n = 7), inability to confirm pathology (n = 2), transplantation procedure with hematopoietic basis (n = 1), and duplicate patient treated at two institutions (n = 1). Each respective university performed pathologic review of their patients with PTLD; assessment of tissue Epstein-Barr virus (EBV) status was performed through in situ hybridization (EBER) staining at each institution. Staging evaluations and therapy for PTLD were completed at the discretion of the patients' individual treating physicians.

Statistical Analysis

Covariates were collected as listed in Table 1 and comprised the data set on which univariate analyses for progression-free survival (PFS) and overall survival (OS) were performed. PFS was calculated from the date of PTLD diagnosis to date of death or disease relapse/progression. OS was computed from the date of PTLD diagnosis to the date of death or last follow-up. Survival analyses were performed regardless of amount or length of therapy received. Three-year PFS and OS rates were estimated through the Kaplan-Meier method,[25] whereas survival differences were assessed by using the log-rank test. Univariate associations between clinical and laboratory factors and survival were derived by using Cox proportional hazards model.[26] Variables with a P value $\leq$ .05 in univariate analyses were entered onto the multivariate Cox proportional hazards model in a stepwise fashion.[27] Hazard ratios (HRs) and their 95% CIs were reported. By using significant factors identified in multivariate analysis, a prognostic model for survival was constructed by classification and regression tree (CART) analysis. The presence of each variable was assigned one point, and the sum of the variables constituted the final score. Prognostic factors were summed for each patient and then were categorized by that sum. All statistical analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Baseline disease and patient characteristics with associated univariate risk of PFS and OS are presented in Table 1. The most common SOT was kidney (58%, including kidney alone and kidney/pancreas). The median time from organ transplantation to PTLD diagnosis was 48 months (range, 2 to 216 months). Thirty-one (39%) of the 80 patients with PTLD diagnoses occurred early ($\leq$ 12 months from SOT), whereas 12 patients (15%) were diagnosed more than 10 years after SOT. On the basis of EBV status, median time to PTLD diagnosis for EBV-positive patients was 11.5 months (range, 2 to 216 months), whereas time to diagnosis for EBV-negative patients with PTLD was 69 months (range, 2 to 192 months; P = .002). In addition, 22 (73%) of 30 patients with PTLD that occurred within a year of transplantation were EBV positive compared with 17 (34%) of 50 patients with late PTLD (P = .0011). Monomorphic occurrences were similarly distributed among patients with EBV-negative PTLDs (20 [69%] of 29 patients) and EBV-positive PTLDs (24 [62%] of 39 patients). Among all patients, nearly one third presented with PS $\geq$ 2, 13% had CNS disease (all primary), 35% had greater than one extranodal site, and two thirds had elevated lactate dehydrogenase (LDH).

The characteristics most associated with risk of progression and OS on univariate analyses were PS, bone marrow (BM) involvement, CNS involvement, extranodal disease, and hypoalbuminemia (Table 1). Elevated LDH was of borderline significance. With only patients who had monomorphic disease (n = 54) included in univariate analysis, similar hazard ratios were noted among the same variables (data not shown).

Treatment

Treatment patterns were reported by EBV status, histologic subtype, and treatment received (Fig 1). All patients had RI as an initial component of therapy, whereas 64 (80%) of 80 patients received rituximab at some point during treatment. Moreover 59 (74%) of 80 patients received rituximab-based therapy concurrently with RI as initial treatment. EBV-positive PTLD patients (n = 39) who received single-agent rituximab appeared to have lower risk of disease (six of 15 patients with International Prognostic Index (IPI) of 3 to 5, and two of 15 patients with bulky disease $>$ 5 cm) compared with rituximab plus chemotherapy–treated patients (nine of 14 patients with IPI 3 to 5, and nine of 14 patients with bulk $>$ 5 cm). Three of eight patients with EBV-negative disease (n = 28) who received single-agent rituximab had IPI 3 to 5, and two of eight had disease greater than 5 cm, whereas nine of 14 patients who received rituximab and chemotherapy had IPI 3 to 5, and 10 of 14 had bulky disease greater than 5 cm. Five patients treated with first-line, single-agent rituximab had stable disease (two EBV positive, two EBV negative, 1 unknown) and received second-line chemotherapy to achieve complete response. Fourteen of the 21

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Table 1. Baseline Patient and Disease Characteristics With Univariate Analysis

Variable	Patients		Survival					
			PFS			OS		
	No.	%	Hazard Ratio*	95% CI	*P*	Hazard Ratio*	95% CI	*P*
Organ transplanted								
Kidney	37	46						
Kidney-pancreas	9	12						
Pancreas	4	5	0.74	0.38 to 1.46	.39	0.69	0.33 to 1.45	.96
Liver	17	21						
Heart	8	10						
Lung	5	6						
Age, years								
≤ 45	44	55	1.39	0.69 to 2.77	.35	1.56	0.72 to 3.35	.26
> 45	36	45						
Diagnosis								
1998-2003	27	34	1.14	0.56 to 2.29	.72	1.17	0.55 to 2.48	.68
2004-2008	53	66						
PTLD								
Early†	31	39	1.01	0.50 to 2.05	.97	0.95	0.44 to 2.04	.89
Late†	49	61						
Histology								
Monomorphic‡	54	68	Monomorphic *v* polymorphic 1.34	0.60 to 2.99	0.47	2.11	0.80 to 5.57	.13
Polymorphic	22	27	Monomorphic *v* plasmacytic/reactive, 1.19	0.29 to 5.1	0.54	2.14	0.29 to 8.65	.26
Plasmacytic/reactive	4	5	Polymorphic *v* plasmacytic/reactive, 0.89	0.19 to 4.19	0.54	1.01	0.12 to 8.65	.26
Tumor EBV status								
Positive	39	49						
Negative	28	35	1.17	0.53 to 2.16	0.70	0.88	0.37 to 2.07	.77
Not available	13	16						
Performance score								
0-1	55	69	2.85	1.44 to 5.65	0.003	3.43	1.64 to 7.15	.001
2-4	25	31						
Bone marrow involvement								
Absent	57	71						
Present	12	15	3.56	1.59 to 7.94	0.002	3.68	1.62 to 8.35	.002
Not available	11	14						
CNS involvement								
No	70	87	2.56	1.10 to 5.95	0.03	2.51	1.01 to 6.22	.04
Yes	10	13						
GI involvement								
No	35	44	1.46	0.72 to 2.97	0.30	1.44	0.66 to 3.11	.36
Yes	45	56						
Extranodal sites present								
≤ 1	50	62	1.86	0.95 to 3.65	0.07	2.12	1.02 to 4.39	.044
> 1	28	35						
Not available	2	3						
Stages III to IV disease	53	66	1.12	0.53 to 2.34	0.77	1.21	0.54 to 2.74	.65
IPI								
0-2	44	55	2.04	0.99 to 4.18	.053	1.76	0.81 to 3.86	.16
3-5	33	41						
Not available	3	4						
Bulky disease§								
No	50	62	0.96	0.48 to 1.92	.91	1.13	0.54 to 2.36	.75
Yes	30	38						
Hemoglobin, g/dL								
≥ 10	40	50	0.95	0.46 to 1.94	.88	0.97	0.44 to 2.13	.94
< 10	37	46						
Not available	3	4						

(continued on following page)

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Table 1. Baseline Patient and Disease Characteristics With Univariate Analysis (continued)

Variable	Patients		Survival					
			PFS			OS		
	No.	%	Hazard Ratio*	95% CI	*P*	Hazard Ratio*	95% CI	*P*
LDH								
Normal	28	35	1.63	0.75 to 3.52	.22	2.27	0.92 to 5.60	.08
Elevated	50	62						
Not available	2	3						
Albumin								
Normal	23	29	2.51	1.03 to 6.11	.04	4.60	1.39 to 15.27	.01
Low	56	70						
Not available	1	1						

Abbreviations: PTLD, post-transplantation lymphoproliferative disease; EBV, Epstein-Barr virus; GI, gastrointestinal; IPI, International Prognostic Index.
*Hazard ratios > 1 indicate a factor with poor prognosis, whereas hazard ratios < 1 indicate a factor with favorable prognosis.
†Early is < 1 year; late is 1 year or greater.
‡Includes 49 patients with diffuse large B-cell lymphoma, two with Burkitt/Burkitt-like disease, two with T-cell lymphoma (one γ-δ disease and one not otherwise specified), and one with Hodgkin lymphoma-type disease.
§Bulky disease is > 5 cm.

patients who did not receive first-line rituximab-based therapy had CD20–positive disease. By classification, 14 of these patients had B-cell PTLD (monomorphic, n = 9; polymorphic, n = 5); the remaining seven patients had plamacyctic/reactive disease (n = 4), T-cell lymphoma (n = 2), and Hodgkin's lymphoma (n = 1). Treatment of these patients is depicted in Figure 1.

Regarding modulation of RI, patients who received chemotherapy (with or without rituximab; n = 46) had a mean decrease of immunosuppressive therapy during chemotherapy by 80% (median, 90%; range, 33% to 100%). Patients who received single-agent rituximab (n = 26) had a mean RI reduction of 54% (median, 55%; range, 0% to 100%; *P* = .04). Of the 21 patients who did not receive rituximab as a component of initial therapy, 16 experienced progression, and 14 died. Five of the 21 patients received rituximab as a part of salvage therapy (second-line or beyond); three of these five patients experienced progression and died.

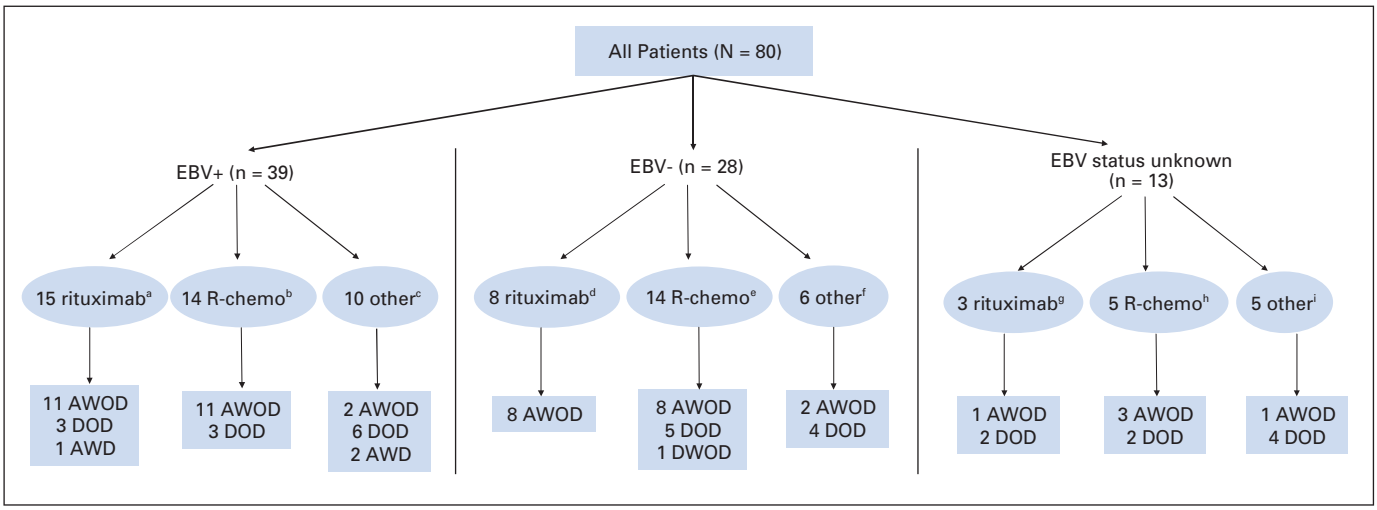

Fig 1. Initial therapy and outcomes by Epstein-Barr virus (EBV) status. Treatment patterns of each patient with post-transplantation lymphoproliferative disease (PTLD) are reported by EBV status, histologic subtype, and therapy received. Therapy received is described as rituximab based (ie, single-agent rituximab or rituximab/chemotherapy); non-rituximab treatment as first-line therapy is classified as other. (a) One patient had partial response (PR) and received R-CHOP, whereas one patient had PR and received radiation. (b) R-chemotherapy (R-chemo) regimens were as follows: R-CHOP (n = 7); R-systemic methotrexate (eg, R-MPV, n = 4); R-ProMACE-CytaBOM (n = 1); R-CODOX-M/IVAC (n = 1); and R-cyclophosphamide/prednisone (n = 1). (c) Other regimens were as follows: immunosuppression reduction alone (n = 5); ProMACE-CytaBOM (n = 3); cyclophosphamide/prednisone (n = 1); bortezomib/dexamethasone (n = 1). (d) One patient had surgery and rituximab, whereas one patient had stable disease (SD) and received R-CHOP. (e) R-chemotherapy regimens were as follows: R-CHOP (n = 12); R-nitrogen mustard (n = 1); and R-cyclophosphamide (n = 1). (f) Other regimens were as follows: VAD (n = 2); radiation (n = 1); cyclophosphamide with radiation (n = 1); unknown chemotherapy (n = 1); and fludarabine (n = 1). (g) One patient had PR and had subsequent surgery (skin lesions). (h) R-chemotherapy regimens were as follows: R-CHOP (n = 3); R-ProMACE-CytaBOM + interferon (n = 1); and R-methotrexate, temozolomide + radiation therapy (n = 1). (i) Other regimens were as follows: immunosuppression reduction alone (n = 2); CHOP (n = 1); ProMACE-CytaBOM + interferon (n = 1); and cytarabine (n = 1). R-chemotherapy, rituximab-chemotherapy; AWOD, alive without disease; DOD, dead as a result of disease; AWD, alive with disease; DWOD, dead without disease; R-CHOP, ritxuimab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-MPV, rituximab, methotrexate, procarbazine, and vincristine; R-ProMACE-CytaBOM, rituximab, prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin,vincristine, and methotrexate; R-CODOX-M/IVAC, rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine; VAD, vincristine, adriamycin, and dexamethasone.

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Outcomes

During a 40-month median follow-up, 3-year PFS for all patients was 57% (95% CI, 45% to 68%), and 3-year OS was 62% (95% CI, 50% to 72%), as shown in Figure 2A; this was apparent despite 13 of 80 patients who died ≤ 6 weeks from the time of PTLD diagnosis, primarily as a result of disease progression. Characteristics of these 13 patients included the following: nine of 13 were older than 45 years of age; nine had kidney-based SOT (n = 1 each for heart, lung, liver, and pancreas); four of 13 had CNS disease; and six had EBV-positive PTLD (whereas 1 was EBV negative, and six were unknown EBV status). Treatment consisted of the following: chemotherapy (n = 4), RI alone (n = 4), rituximab with chemotherapy (n = 3), and single-agent rituximab (n = 2). Among patients with monomorphic PTLD (n = 54), 3-year PFS and OS were 55% (95% CI, 42% to 69%) and 57% (95% CI, 40% to 68%), respectively, compared with polymorphic disease 3-year PFS and OS rates of 61% (95% CI, 37% to 78%) and 76% (95% CI, 54% to 88%), respectively.

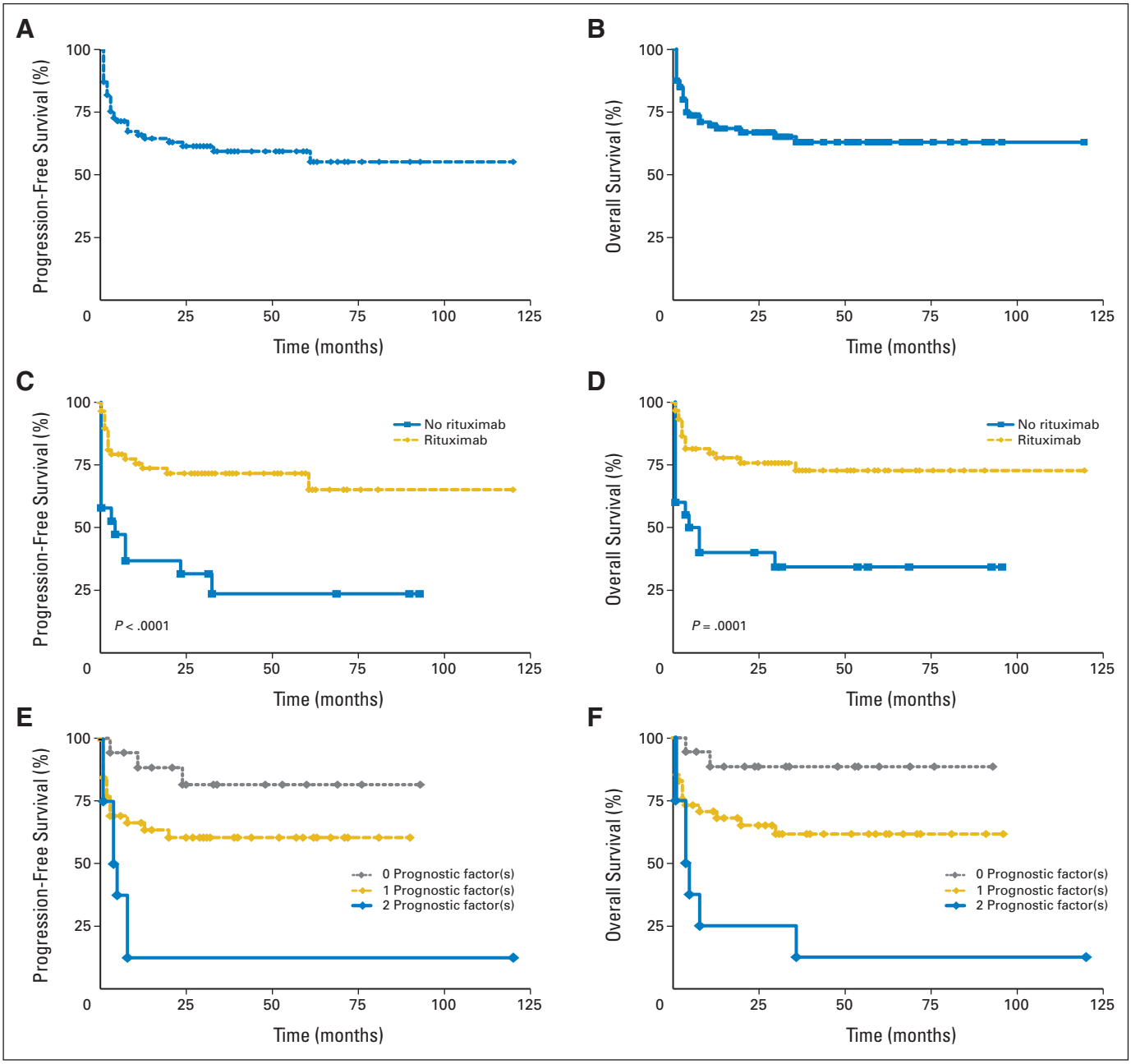

Fig 2. Progression-free survival (PFS) and overall survival (OS) and prognostic survival model. PFS and OS for all patients. Kaplan-Meier curves of (A) PFS and (B) OS in 80 patients with post-transplantation lymphoproliferative disease. Kaplan-Meier curves of (C) PFS and (D) OS in the 59 patients with PTLD who received rituximab-based therapy compared with the 21 patients who did not receive rituximab as a component of initial therapy was associated with significantly improved PFS ($P < .0001$) and OS ($P = .0001$) for the former cohort. Kaplan-Meier curves of (E) PFS and (F) OS for patients with PTLD on the basis of number of the adverse prognostic factors present (ie, hypoalbuminemia and/or bone marrow involvement at PTLD diagnosis). Increasing number of factors presented portended an increasingly poor prognosis: 3-year PFS with 0, 1, or 2 factors: 82%, 68%, and 11%, respectively ($P < .0006$), and 3-year OS rates of 89%, 62%, and 11%, respectively ($P < .0001$).

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Table 2. Prognostic Factors With Associated 3-Year Survival Rates Using Univariate Analysis

Variable	No. of Patients	Survival					
		PFS			OS		
		3-Year Rate (%)	95% CI	*P*	3-Year Rate (%)	95% CI	*P*
Performance status							
0-1	55	67	52 to 78	.0012	73	59 to 83	.0003
2-4	25	36	18 to 54		35	15 to 56	
Received first-line rituximab-based therapy				< .0001			.0001
No	21	21	7 to 42		33	14 to 53	
Yes	59	70	57 to 81		73	58 to 83	
Albumin				.03			.005
Normal	56	76	52 to 90		86	62 to 95	
Low	23	50	36 to 62		53	38 to 65	
CNS involvement				.02			.03
Absent	70	61	48 to 72		65	52 to 76	
Present	10	30	7 to 58		40	12 to 67	
Bone marrow involvement				.0007			.0006
Absent	57	66	51 to 77		71	57 to 81	
Present	12	18	3 to 44		18	3 to 44	
> 1 extranodal site				.06			.03
No	50	64	48 to 76		72	57 to 82	
Yes	28	42	24 to 59		43	23 to 61	

NOTE. The 3-year PFS and OS by Kaplan-Meier analysis are reported with their associated 95% CIs.
Abbreviations: PFS, progression-free survival; OS, overall survival.

Overall, 34 patients experienced disease progression, and the overwhelming majority of relapses (91%) occurred within 1 year from PTLD diagnosis. Table 2 shows 3-year survival rates that were based on the prognostic factors identified on univariate analysis. According to treatment received, 3-year PFS and OS for patients who received first-line rituximab-based therapy (n = 59) were 70% and 73%, respectively, compared with 21% and 33% among patients who did not receive rituximab as a component of initial therapy (PFS, $P < .0001$; OS, $P = .0001$). If only patients who received first-line rituximab-based therapy (n = 59) were analyzed in univariate analysis, only poor PS (ECOG 2 to 4) significantly predicted for PFS and OS, whereas IPI and CNS disease were borderline (Appendix Table A1, online only).

Multivariate Analysis and Survival Model

Multivariate Cox regression analysis was performed by using the significant prognostic factors identified in univariate analysis. Hypoalbuminemia, CNS involvement, greater than one extranodal site, and the use of rituximab-based treatment maintained prognostic significance for PFS and OS on multivariate analysis (Table 3). The inclusion of treatment (ie, rituximab) in this analysis was associated with bias, because therapy was not predetermined or uniform. When rituximab was removed from the multivariate model (ie, including only objective covariates), CNS involvement and hypoalbuminemia retained their prognostic value, whereas BM involvement replaced greater than one extranodal site (Table 3). A survival model was

Table 3. Multivariate Analyses of Prognostic Factors

Prognostic Factor	Survival					
	PFS			OS		
	Hazard Ratio*	95% CI	*P*	Hazard Ratio*	95% CI	*P*
Model including treatment as a variable (n = 80)†						
Received rituximab-based therapy†	0.23	0.10 to 0.55	.0009	0.21	0.08 to 0.53	.0009
CNS involvement	5.66	1.61 to 19.97	.007	3.88	1.09 to 13.86	.04
> 1 extranodal site	2.59	1.07 to 6.28	.04	2.14	0.87 to 5.31	.10
Hypoalbuminemia	2.67	0.86 to 8.26	.09	3.93	1.10 to 14.07	.04
Model *P*		< .0001			< .0001	
Model excluding treatment as a variable (n = 80)						
CNS involvement	4.70	1.45 to 15.20	.0099	3.61	1.06 to 12.32	.04
Bone marrow involvement	2.95	1.13 to 7.68	.03	3.14	1.14 to 8.65	.03
Hypoalbuminemia	2.96	1.01 to 8.98	.055	3.64	1.05 to 12.60	.04
Model *P*		.0004			.0003	

Abbreviations: PFS, progression-free survival; OS, overall survival.
*Hazard ratios > 1 indicate a factor with poor prognosis, whereas those < 1 indicate a factor with favorable prognosis.
†Treatment: rituximab-based therapy as a part of first-line post-transplantation lymphoproliferative disease therapy *v* not as part of first-line therapy.

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created by using the variables with significance in multivariate analysis. An increasing number of these three independent variables (ie, hypoalbuminemia, CNS, and BM involvement) was associated with markedly different survival rates: 3-year PFS rates with 0, 1, or ≥ 2 factors were 84%, 66%, and 7%, respectively ($P < .001$); 3-year OS rates were 93%, 68%, and 11%, respectively ($P < .001$). An additional, simplified survival model that used only hypoalbuminemia and BM involvement was associated with similar outcomes, as shown in Figures 2E and 2F.

Toxicity

Detailed adverse events were not available, given the retrospective nature of this project. However, records were examined for occurrence of neutropenic fever and grades 3 to 4 nonhematologic adverse events. Of the 27 patients who received rituximab alone as first-line therapy, toxicities were documented in six patients: gastrointestinal bleed (n = 2), sepsis (n = 2), neutropenic fever (n = 1), and pneumonia (n = 1). Among 45 patients who received first-line chemotherapy (with or without ritxuximab), 25 experienced multiple treatment-related toxicities: neutropenic fever (n = 19), acute renal failure (n = 10; six related to sepsis, and two related to tumor lysis syndrome), sepsis (n = 8), pneumonia (n = 5), bowel perforation (n = 5), mucositis (n = 2), cellulitis (n = 2), idiopathic thrombocytopenic purpura (n = 2), osteomyelitis (n = 1), and cardiomopathy (n = 1). There were no apparent toxicity differences among patients who received chemotherapy alone compared with rituximab plus chemotherapy (data not shown). One patient treated with RI alone had sepsis.

Sixteen patients (19%) experienced rejection of their transplanted organ either during or within 12 months of completion of therapy (Table 4). The median time from SOT to rejection was 30 months (range, 2 to 70 months). Organs rejected were kidney (n = 8), liver (n = 3), pancreas (n = 2), and kidney/pancreas, heart and lung (n = 1 each). Five episodes were mild and resolved, whereas 11 resulted in organ failure. Three-year PFS and OS rates for these patients were 50% and 56%, respectively. Comparisons were made for each respective variable compared with patients who had PTLD without rejection. The only factors associated with organ rejection were late PTLD (ie, > 1 year after SOT) and patients who received chemotherapy (at any point). Of note, the degree of change in RI was not different for patients who experienced rejection (mean decrease, 69%; median, 90%; range, 0% to 100%) compared with patients without rejection (mean decrease, 69%; median, 75%; range, 0% to 100%).

Table 4. Characteristics of Patients With PTLD Who Experienced Graft Rejection

Characteristic	Patients (N = 16) No.	%	P*
Rejected organ			
Kidney†	9	56	.99
Age, years			
> 45	6	38	.58
Late PTLD‡	9	56	.042
Histology			
Polymorphic*	7	44	.12
Tumor EBV status			
Positive	10	62	.78
Performance score			
2-4	4	25	.99
Bone marrow involvement			
Involved	3	19	.99
CNS involvement			
Yes	1	6	.45
GI involvement			
Yes	9	56	.99
Extranodal sites present			
> 1	7	44	.99
Stages III and IV disease	11	69	.99
IPI			
3-5	5	31	.40
Bulky disease§			
Yes	7	44	.58
Hemoglobin, g/dL			
< 10	10	62	.26
LDH			
Elevated	8	50	.15
Albumin			
Low	13	81	.37
Chemotherapy as initial therapy	11	69	.40
Rituximab-based initial therapy	12	75	.99
Chemotherapy at any point of treatment	14	88	.025

Abbreviations: PTLD, post-transplantation lymphoproliferative disease; EBV, Epstein-Barr virus; GI, gastrointestinal; IPI, International Prognostic Index.
*Fisher's *P* value indicates comparison with same factor in patients without organ rejection.
†Includes one patient who underwent synchronous kidney/pancreas transplantation.
‡PTLD at > 1 year.
§Bulky disease is > 5 cm.

DISCUSSION

The pathologic spectrum of PTLD is heterogenous, although the majority of patients are classified as monomorphic subtype. Historically, PTLD was reported to occur at a median of 6 months from SOT (80% within 1 year),[28] although recent data suggest this interval is longer.[6,18,19,21] Patients with early PTLD more often express EBV, whereas late-onset disease (ie, > 12 months after SOT) is typically EBV negative.[8,12,29] Among 80 patients with SOT-related PTLD treated at four centers over a recent 10-year period, we found a median time from SOT to PTLD diagnosis of 48 months, with 61% of diagnoses occurring after 1 year and 15% at 10 years after SOT. EBV-negative disease constituted 42% of patients (for which EBV status was known), which likely reflected the longer time to PTLD diagnosis.[8,29] Nelson et al[12] showed the incidence of EBV-negative diseases were significantly increased after 1990 versus before 1990 (23% *v* 2%, respectively; $P < .001$), possibly as a result of changing immunosuppressive regimens as well as improved diagnostic techniques. Similar to other published reports, we found a shorter time to PTLD (ie, 11.5 months) among patients with EBV-positive disease.

Therapy of PTLD is not standardized, and treatment strategies often are tailored to specific clinical settings because of the particular SOT graft, risk of rejection, associated comorbidities, and tumor burden/disease presentation. Treatment options include RI, chemotherapy, rituximab, surgery, and radiation, or a combination of these approaches. A long-standing PTLD treatment paradigm has been to initially proceed with RI alone,[13] which is associated with complete remission rates of 0% to 50%.[5,9,14,30,31] Clinical factors associated with lack of response to RI include late-onset PTLD, elevated LDH, organ dysfunction, and multiorgan involvement.[14,30,31] Unfortunately,

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these are common disease manifestations among patients with PTLD; in addition, responses to RI alone are durable in only 5% to 30% of patients.[5,9,14,30]

Rituximab has been evaluated as a therapy for PTLD in phase II studies and small case series,[10,18,19,21-23,32,33] although it has been used primarily as a salvage therapy utilized after failure of RI (or later). In two, phase II studies of single-agent rituximab for patients who failed RI, the 1- and 2-year PFS were 30%[12] and 42%,[19] respectively. In the latter trial, Gonzalez-Barca et al[19] administered a second 4-week course of rituximab for patients without complete remission and found an intent-to-treat complete remission rate of 61%.[19] Elstrom et al[22] studied patients who received rituximab-based therapy after RI failure. The overall response rate was 68% (complete remission, 59%) for 22 patients treated with single-agent rituximab, and median OS was 31 months; EBV positivity predicted response to rituximab ($P = .014$). Scant data are available that use rituximab as first-line therapy. Furthermore, few studies have evaluated the combination of rituximab with chemotherapy as first-line treatment for PTLD.[20,34]

In this analysis, therapy was at the discretion of the treating physicians, although RI was universally applied. Furthermore, front-line treatment included rituximab-based therapy, in conjunction with RI, for 74% of patients. Patients with bulky disease and high IPI more often received combined chemotherapy and rituximab versus rituximab alone. In addition, RI was decreased to a greater extent for patients who received rituximab and chemotherapy during treatment, in part to prevent infectious complications. However, infectious complications and other toxicities associated were still frequent, especially with chemotherapy, and this was a similar finding to other PTLD reports.[14,22,35] Donor organ graft rejection with PTLD treatment has been poorly described. We identified a surprisingly high rate of solid-organ rejection, and the two most common associated factors were late PTLD and use of chemotherapy. Nonetheless, we identified 3-year PFS and OS rates for all patients of 57% and 62%, respectively. Moreover, patients who received first-line rituximab-based therapy had 3-year PFS and OS rates $\geq$ 70%. In addition, with 40-month median follow-up, only 9% of relapses in our series occurred beyond 1 year. This striking survival plateau has not been noted previously.

Our report confirms several prior observed prognostic factors (eg, presence of CNS disease)[5,11,22,36] but also identifies new factors. Prior studies showed that EBV negativity and late PTLDs were associated with inferior survival.[8,29,37] Additional factors shown to correlate with outcome include extranodal disease, PS, stage, number of disease sites, and LDH.[9,11,21,38,39] On Cox regression multivariate analysis, with treatment removed from the model, we identified CNS involvement, hypoalbuminemia, and BM involvement as the most significant prognostic variables. By using these factors, we formed a survival model that predicted markedly different patient outcomes. An additional simplified model was constructed that included only BM involvement and hypoalbuminemia.

There are several potential explanations of why prognostic factors in PTLD have varied from series to series. First, most PTLD treatment reports have been single-institution studies that examined outcomes over several decades (ie, $>$ 20 to 40 years), during which diagnostic techniques, treatment regimens, and supportive care measures have changed greatly. Second, PTLD series often include heterogenous patient populations. As an example, among the recent series by Knight et al,[5] 22% of patient diseases included Hodgkin's lymphoma, plasmacytoma, and mucosa-associated lymphoid tissue lymphoma histology, and 32% of patients were pediatric. Studies of pediatric patients with PTLD have reported improved outcomes compared with adult patients.[36,40,41] Third, treatment approaches for patients with PTLD have varied, and few have evaluated rituximab as part of first-line management. Interestingly, it appeared that use of early rituximab-based therapy may overcome the adverse prognostic importance of BM involvement and hypoalbuminemia, although this needs to be confirmed in future PTLD studies. Fourth, different characteristics have been included in prognostic analysis. Serum albumin has been shown to be a prognostic factor associated in hematologic malignancies[42-44]; however, hypoalbuminemia has not been examined previously as a prognostic factor in PTLD.

In summary, we found among a large multicenter cohort of patients with PTLD, that the use of rituximab-based therapy in conjunction with RI was associated with significantly improved survival compared with prior reports. This may be related to the use of rituximab-based therapy as first-line therapy (rather than as rescue therapy after failure of RI) in addition to improved supportive care measures. The vast majority of relapses were confined to the first year after PTLD diagnosis, and durable remissions were observed thereafter. Multivariate analysis identified variables predictive of outcome, and a simplified survival model that was based on two clinical factors was constructed; risk-stratified OS rates ranged from 89% to 11%. Furthermore, this is the first paper to identify low albumin as a strong adverse prognostic factor in PTLD. Clinical and tissue-based studies with prospective evaluation of rituximab-based therapy and prognostic factor analyses through multicenter and multinational collaborations are warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Andrew M. Evens, Irene Helenowski, Beverly Nelson, Sonali M. Smith
Financial support: Andrew M. Evens
Administrative support: Andrew M. Evens
Provision of study materials or patients: Andrew M. Evens, Kevin A. David, Dixon Kaufman, Sheetal M. Kircher, Alla Gimelfarb, Elise Hattersley, Patrick Stiff, Jane N. Winter, Jayesh Mehta, Koen Van Besien, Stephanie Gregory, Leo I. Gordon, Jamile M. Shammo, Scott E. Smith, Sonali M. Smith
Collection and assembly of data: Andrew M. Evens, Kevin A. David, Irene Helenowski, Sheetal M. Kircher, Alla Gimelfarb, Elise Hattersley,

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Lauren A. Mauro, Borko Jovanovic, Jamile M. Shammo, Scott E. Smith, Sonali M. Smith

Data analysis and interpretation: Andrew M. Evens, Kevin A. David, Irene Helenowski, Beverly Nelson, Dixon Kaufman, Borko Jovanovic, Amy Chadburn, Jamile M. Shammo, Scott E. Smith, Sonali M. Smith

Manuscript writing: Andrew M. Evens, Kevin A. David, Irene Helenowski, Beverly Nelson, Dixon Kaufman, Borko Jovanovic, Amy Chadburn, Jamile M. Shammo, Scott E. Smith, Sonali M. Smith

Final approval of manuscript: Andrew M. Evens, Kevin A. David, Irene Helenowski, Beverly Nelson, Dixon Kaufman, Sheetal M. Kircher, Alla Gimelfarb, Elise Hattersley, Lauren A. Mauro, Borko Jovanovic, Amy Chadburn, Patrick Stiff, Jane N. Winter, Jayesh Mehta, Koen Van Besien, Stephanie Gregory, Leo I. Gordon, Jamile M. Shammo, Scott E. Smith, Sonali M. Smith

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